

REMARKS

At the interview, Applicant proposes to discuss why the subject matter encompassed by the proposed amended claims would not have been obvious to one of skill in the art from the cited art as represented by the primary reference to Chaplin et al, either alone or in combination with the cited secondary references. Among other things, Applicant proposes to discuss why the cited art would not have provided even a reasonable expectation of success that a NOS inhibitor could augment (rather than decrease) the effect of a tubulin binding agent that is used to cause damage to neovasculature. In particular, Applicant will discuss the teachings of Chaplin et al in line with the following:

The paper is split into two sections:

- (i) Reversible modulation of tumor blood flow, primarily using vasoactive drugs. These approaches could be used to **either increase or decrease** blood flow selectively to the tumor. The potential benefits of transiently increased tumor blood flow described are improved delivery of systemic agents and improved oxygenation. The potential benefits of transiently decreased blood flow described are (a) enhancing the activity of agents that are more toxic in a hypoxic or acidic environment, and (b) manipulating drug pharmacokinetics, i.e. to increase the exposure time of tumor cells to anti-cancer agents.
- (ii) Irreversible reduction in tumor blood flow caused by vascular targeting agents, resulting in prolonged ischaemia and extensive tumor cell death.

From this paper one of skill in the art could not predict whether there would be a

benefit (as opposed, for example, to a detriment) of combining a vascular targeting agent which causes irreversible reductions in tumor blood flow, with a NOS inhibitor, which under some (but not all) conditions may act as a reversible inhibitor of tumor blood flow.

At the interview, Applicant also proposes to discuss the documents annexed to the Information Disclosure Statement filed 14 January 2005 which, in connection with the evidence in the specification of this application, provide evidence of unexpectedly advantageous results with the claimed invention that would be sufficient to rebut any alleged *prima facie* case of obviousness set forth by the cited art.

Respectfully submitted,

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